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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,311	03/22/2004	John Hermon-Taylor	117-501	9576

23117 7590 01/18/2006

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EXAMINER	
ZEMAN, ROBERT A	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 01/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/805,311	HERMON-TAYLOR ET AL.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *51-73* is/are pending in the application.

4a) Of the above claim(s) *66-69* is/are withdrawn from consideration.

5)☒ Claim(s) *73* is/are allowed.

6)☒ Claim(s) *51-65 and 70-72* is/are rejected.

7)☒ Claim(s) *51,63 and 72* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 March 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3-22-2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment and response filed on 11-22-2005 are acknowledged. Claims 51, 63 and 66-68 have been amended. Claims 49-50 have been canceled. Claims 70-73 have been added. Claims 51-73 are pending. Claims 66-69 remain withdrawn from consideration as being drawn to non-elected inventions. Claims 51-65 and 70-73 are currently under examination.

Information Disclosure Statement

The remaining references cited on the Information Disclosure Statement filed on 3-22-2004 have been considered. An initialed copy of said Information Disclosure Statement is attached hereto.

Drawings

New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because the drawings submitted on 3-22-2004 are not in compliance with 37 C.F.R. 1.121 which requires any replacement drawing sheet to be identified as a "Replacement Sheet" in the top margin. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Priority

Applicant's claim to priority is deemed perfected in light of the amendment to the specification filed on 3-22-2004.

Election/Restrictions

Applicant's request for rejoinder of the withdrawn method claims is noted. However, since there are no allowed claims to date, rejoinder of said claims would be premature.

Objections Withdrawn

The objection to the Title as being non-descriptive is withdrawn in light of the amendment thereto. It is suggested however, that the protein that is engendered by SEQ ID NO:24 be included in the title.

Objections Maintained

The objection to the specification for the recitation of trademarks/tradenames is maintained. Applicant's amendment to the specification is insufficient to overcome this objection as the specification still contains improper tradenames/trademarks (see pages 7, 29 and 37 for example).

New Claim Objections

Claim 51, 63 and 72 are objected to because of the following informalities: claims 51 and 63 contain some obvious errors. Firstly, part (a) of claim 51 refers to a polynucleotide

encoding the polypeptide of SEQ ID NO:**23**. SEQ ID NO:23 is a nucleic acid sequence. Based on Applicant's election, the specification and claim 72 it is obvious that Applicant meant SEQ ID NO:24. Secondly, claims 51 and 72 in part (c) and claim 63 in part (b) contain an obvious error in that they refer to polynucleotides having homology over contiguous **amino acids**. It is obvious from the language of said claim and in light of the specification that Applicant meant "nucleotides". Appropriate correction is required.

Claim 72 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 51. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Both claims are drawn to a vector carrying a polynucleotide comprising a polynucleotide encoding the polypeptide of SEQ ID NO:24 (claim 51 in advertently refers to SEQ ID NO:23 – see above); a polynucleotide encoding a fragment of at least 10 amino acids of the polypeptide of SEQ ID NO:24; or a polypeptide having at least 90% homology to the polynucleotide of SEQ ID NO:23 over 30 residues wherein said polynucleotide encodes a polypeptide having the ability to stimulate an immune response against the polypeptide of SEQ ID NO:24.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 51-65 and newly added claim 72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons set forth in the previous Office action in the rejection of claims 49-65. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant argues:

1. Independent claim 51 is limited to vectors carrying polynucleotides which encode SEQ ID NO:24 and variants thereof which the potential to stimulate an immune response to the polypeptide of SEQ ID NO:24.

2. The instant claims do not require an immune response to be directed against a bacterium.

3. The skilled reader could determine the like sites of immunogenicity within the sequence of SEQ ID NO:24 and could select fragments or variants (as defined in parts (b) and (c) of claim 51) which retain those immunogenic regions and therefore would be expected to be able to stimulate an immune response against SEQ ID NO:24.

4. In order to produce a vector according to part (b) or (c) of claim 51 it is not necessary to carry out a complete structural characterization of the molecular interface between the antigen and antibody as suggested by Greenspan. One only needs to determine the like sites of immunogenicity within the sequence of SEQ ID NO:24 and retain those immunogenic regions when creating variant sequences.

5. The reference by Meister et al. discloses that algorithms can be used to scan amino acid sequences for potential epitope regions and that their use was a common procedure at the time the invention was made.

Applicant's arguments have been fully considered and deemed persuasive.

The rejected claims are drawn to polynucleotides (and vectors carrying said polynucleotides) that encode a polypeptide capable of stimulating an immune response the polypeptide of with the sequence set forth in SEQ ID NO:24. In other words, the immune response generated is to the polypeptide of SEQ ID NO:24, not necessarily to the polypeptide encoded by the polynucleotide.

Neither the exemplary embodiments nor the general method disclosed in the specification appears to describe structural features, in structural terms that are common to the genus. That is, the specification provides neither a representative number of species (immunoepitopes specific for a directed immune response to the polypeptide of SEQ ID NO:24) to describe the claimed genus, nor does it provide a description of structural features that are common to species (immunoepitope). As discussed above, the specification provides no structural description of immunoepitopes other than ones specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed polypeptide/polynucleotide looks like. The specification's disclosure is inadequate to describe the claimed genus of polynucleotides (and vectors carrying said polynucleotides) that encode a polypeptide capable of stimulating an immune response the polypeptide of with the sequence set forth in SEQ ID NO:24. Applicant's arguments are all predicated on the belief that it would be

easy for the skilled artisan to determine which immunoepitopes would direct an immune response to the polypeptide of SEQ ID NO:24 and simply maintain them within a given "variant". In fact it seems that Applicant's argument supports the Examiner's position that Applicant was not in possession of the claimed invention. Moreover, Applicant is reminded that MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and **adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.** See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016. Hence, only the polynucleotides encoding the polypeptide with the sequence set forth in SEQ ID NO:24 meets the written description requirement.

As outlined previously, the claims are drawn to a vast genus of polynucleotides wherein said polynucleotide comprises SEQ ID NO:23, has at least 90% homology to SEQ ID NO:23 over 30 nucleotides (note that the claims recite "amino acids" but the limitation is being interpreted to read on nucleotides –see objection above), encodes the polypeptide of SEQ ID

NO:24 or a fragment of at least 10 amino acids of the polypeptide of SEQ ID NO:24. All said polynucleotides must be able to stimulate an immune response to the polypeptide encoded by the sequence set forth in SEQ ID NO:24. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession the claimed invention. To adequately describe the genus of polynucleotides (as described above) that stimulate an immune response to a the polypeptide of SEQ ID NO:24, Applicant must adequately describe the antigenic determinants (immunoepitopes) that elicit an immune response directed against the polypeptide of SEQ ID NO:24 not just those determinants that would elicit an immune response to the polypeptide encoded by said polynucleotide. A given polypeptide can be immunogenic but not induce an immune response directed against a given polypeptide wherein said polypeptide comprises a different amino acid sequence.

However, the specification does not disclose distinguishing and identifying features of a representative number of members of the genus of polynucleotides (or the polypeptides they encode) to which the claims are drawn, such as a correlation between the structure of the immunoepitope and its recited function (to elicit an immune response directed against the polypeptide of SEQ ID NO:24), so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus of polynucleotides.

Moreover, the specification fails to disclose which amino acid residues of the encoded polypeptides are essential to the function of the immunoepitope or which amino acids might be replaced or deleted so that the resultant immunoepitope retains the activity of its parent, or by which other amino acids the essential amino acids might be replaced so that the resultant immunoepitope retains the activity of its parent. Therefore, since the specification fails to adequately describe at least a substantial number of members of the genus of immunoepitopes to which the claims are based; the specification fails to adequately describe at least a substantial number of members of the claimed genus of polynucleotides capable of stimulating an immune response to a the polypeptide of SEQ ID NO:24.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and **adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.** See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112,

paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossessionl may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus.

As evidenced by Greenspan et al. (*Nature Biotechnology* **7**: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the

structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit an immune response to a given pathogen can only be identified empirically. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of immunoepitopes, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of immunogenic compositions capable of stimulating an immune response in an animal *to* a mycobacterium (as opposed to the polypeptide encoded by the polynucleotide) Therefore, because the art is unpredictable, in accordance with the *Guidelines*, the description of immunoepitopes (antigenic determinants) is not deemed representative of the genus of immunogenic compositions to which the claims refer. Hence only the polynucleotides encoding the polypeptide with the sequence set forth in SEQ ID NO:24 meets the written description requirement.

Claims 51-65 and newly added claim 72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polynucleotides with the sequence set forth in SEQ ID NO:23 and those polynucleotides (and vectors carrying said polynucleotides) encoding polypeptides with the sequence set forth in SEQ ID NO:24 wherein said polynucleotides elicit an immune response to SEQ ID NO:24, does not reasonably provide enablement for any other of

the myriad of polynucleotides (and vectors) encompassed by the instant claims . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Applicant argues:

1. In order to produce a vector according to part (b) or (c) of claim 51 it is not necessary to carry out a complete structural characterization of the molecular interface between the antigen and antibody as suggested by Greenspan. One only needs to determine the like sites of immunogenicity within the sequence of SEQ ID NO:24 and retain those immunogenic regions when creating variant sequences.

2. The reference by Meister et al. discloses that algorithms can be used to scan amino acid sequences for potential epitope regions and that their use was a common procedure at the time the invention was made.

The rejected claims are drawn to polynucleotides that encode a polypeptide capable of stimulating an immune response to the polypeptide with the sequence set forth in SEQ ID NO:24 wherein said polynucleotide comprises SEQ ID NO:23, , has at least 90% homology to SEQ ID NO:23 over 30 amino acid residues, encodes the polypeptide of SEQ ID NO:24 or a fragment of at least 10 amino acids of the polypeptide of SEQ ID NO:24.

Applicant's arguments are all predicated on the belief that it would be easy for the skilled artisan to determine which immunoepitopes would direct an immune response to the polypeptide of SEQ ID NO:24 and simply maintain them within a given "variant".

Applicant further cites the reference by Meister et al. as being indicative of the state of the art at the time of the invention and relies on the ability of the disclosed algorithms to provide enablement for the instant claims. Aside from the fact that the use of these essential algorithms are in no way incorporated or disclosed by the specification, the Meister reference itself is lacking. Meister et al. disclose on page 588 of said reference "not all predicted peptides can bind to MHC molecules with high affinity, or to stimulate immune responses both *in vitro* and *in vivo*". Meister et al. further disclose "experimental data confirming the accuracy of MCH-binding motifs both *in vivo* and *in vivo*, as well as data linking predicted peptide epitopes to protective immunity, are still lacking". Consequently, the algorithms disclosed by are not capable, contrary to Applicant's assertion, to predict which "immunoepitopes" would elicit an immune response directed against the polypeptide with the sequence set forth in SEQ ID NO:24.

Additionally, there are an enormous number of polynucleotides, vectors, and host cells to be experimentally tested in order to make a polypeptide with the claimed function. Regarding the polynucleotides to be tested, the art recognizes that for each amino acid in the claimed polynucleotide there are degenerate codons available as shown in the well-known Biochemistry textbook by Lehninger as in Table 31-5 on page 718. Counting the number of codons results in observing that five of the normal amino acids may each be encoded by one of four three-nucleotide codon options. For nine of the normal amino acids, two such three nucleotide-codon options are available. For three amino acids, six such codon options are available. For one amino acid, three such codons are utilized. For two amino acids, only one such codon is available. An average of the number of codons per amino acid may be approximated via an averaging of the above codon usage as being three available codons for an average amino acid. Without

specifying the length of a sequence encoding the claimed fusion proteins, it may be reasonably approximated it is a polypeptide which falls within the range of polypeptides with sizes as shown in the well known Biochemistry textbook by Lehninger as in Table 3-2 on page 57. A median polypeptide contains 550-800 amino acids. Choosing conservatively, a median polypeptide thus contains 500+ amino acids. Therefore, an estimate of the number of potential polynucleotides encoding the claimed proteins of 500 amino acids would be that calculated at 3 raised to the 500^{th} power. This further calculates to approximately 10^{240} possible polynucleotides to evaluate or experimentally test to find those useable in making a useful fusion polypeptide, or a polypeptide meeting the limits of the genus of polypeptides of the instant claims, Thus, there is an enormous number of polynucleotides to experimentally test to find any that encode for a polypeptide with the ability to elicit an immune response directed against the polypeptide with the sequence set forth in SEQ ID NO:24. Antigenicity, or the ability to provoke a specific immune response is strongly dependent on the three dimensional structure of the polypeptide. In the well known Biochemistry textbook by Lehninger at pages 58-62, not only is the vast diversity of protein polypeptides set forth regarding functionality, such as antigenicity, but that each protein has a characteristic three-dimensional shape referred to as its conformation. The specification and claims have not disclosed what portions of the parts of the encoded polypeptide are required for antigenicity, and to test for this factor alone relegates the experimentation to undue experimentation. This experimental search for a test is further complicated by a lack of any guidance regarding what single, or even a subset of polynucleotides out of the 10^{240} should be tested (i.e. which immunoepitopes). These considerations are supportive of a determination of undue experimentation to find a starting material polynucleotide to be placed in a vector and in

turn a host cell for culturing, for production of a polypeptide to be used as claimed.

Turning to the question of what host cell is to be utilized in producing the polypeptide, it is well known that a myriad of thousands of cell types are known to Biotechnology. It is acknowledged that some of these known cell types are more commonly utilized for host cell culturing as described in the specification. Even such commonly utilized host cells number into the hundreds. In U.S. Patent 5,082,767 (Hatfield et al.), the expression of polynucleotides in host cells of various types is described in column 1, lines 1-49. Even though such expression practices are frequently carried out, Hatfield et al describe another major problem in this area in column 1 lines 50-65, wherein a protein (or polypeptide) is produced in recoverable quantities, but is inactive due to unpredictability in proper protein folding during expression. Hatfield et al go on to analyze codon pair usage frequencies wherein optimization of codon pair usage is then derived for determining polynucleotides which encode a protein or polypeptide in order to achieve an active polypeptide when made via a host cell culture such as described herein. This process, however, is complex and requires very specific host cell and polypeptide correspondence in order to perform the analysis to then make a useful and active protein. It is noted that the instant disclosure lacks any codon pair frequency analysis description for even a single host cell type. The Hatfield et al disclosure is a single procedural description that still lacks indication of how someone of skill in the art would test for appropriate antigenicity on which to base the codon usage analysis as disclosed therein. Thus, there would be no predictability as to what to direct a codon pair usage determination to as set forth in Hatfield et al. for the making of an active polypeptide.

This, in summary, the above described unpredictability for polynucleotide testing, or even

what test to perform as well as host cell selection with corresponding codon, codon pair and/or codon context practice is supported by the number into enormous possibilities. No instant guidance to reasonable narrow the required experimentation leads to a determination of undue experimentation being required for both polynucleotide selection, and host cell selection that would result in an active and therefor useful fusion protein of an influenza protein and an unnamed stress protein or variant thereof.

In simple terms, Applicant has failed to demonstrate any polynucleotides (based on SEQ ID NO:23) that encode polypeptides based on SEQ ID NO:24 that are capable of eliciting the claimed immune response (an immune response directed against the polypeptide with the sequence set forth in SEQ ID NO:24 not just to the polypeptide variant or fragment). While the skill in the art of immunology is high, to date, prediction of a specific immune response for any given composition in any given animal is quite unpredictable. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome and form immunoepitopes. Bowie et al. further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (column 1, page 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function

are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Additionally, as evidenced by Greenspan et al. (Nature Biotechnology 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit an immune response to a given pathogen can only be identified empirically. This constitutes undue experimentation. Therefore, given the lack of success in the art, the lack of working examples commensurate in scope to the claimed invention and the unpredictability of the generation of directed immune response, the specification, as filed, does not provide enablement for polynucleotides encoding for polypeptides capable of stimulating an immune response to a mycobacterium. Moreover, it should be noted that the rejected claims read on DNA vaccines but the specification is silent as to what nucleic acids would encode polypeptides that would elicit a protective immune response against the polypeptide with the sequence set forth in SEQ ID NO:24. Hence, the specification is not enabling for the full breadth of the instant claims.

New Grounds of Rejection

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 58-65 and 70-72 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicant has amended the claims 59, 63 and 72 to recite "a polynucleotide having at least 90% sequence homology to the polynucleotide of SEQ ID NO:23 over 30 contiguous amino acid residues". This phrase does not appear in the specification, or original claims as filed. Applicant does not point out specific basis for this limitation in the application, and none is apparent. Page 10 of the specification discloses polynucleotides with at least 90% homology over 40 amino acids and page 9 discloses polynucleotides with at least 80% homology over 30 amino acids. Neither disclosure provides neither explicit nor implicit support for the aforementioned phrase.. Therefore this limitation is new matter.

Conclusion

Claims 51-65 and 70-72 are rejected.

Claim 73 is allowed.

SEQ ID NO:23 and SEQ ID NO:24 are free of the art of record.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov.

Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ROBERT A. ZEMAN
PATENT EXAMINER

January 6, 2006